# Oral Comments to the NTP RoC Board of Scientific Counselors: **Styrene Mode of Action**

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# NTP Draft Substance Profile Mode of Action: Mouse Lung Tumors

NTP Draft Substance Profile Hypothesis:

Styrene metabolism to styrene-7,8-oxide

(SO) with resulting genotoxicity, cytotoxicity and late developing tumors

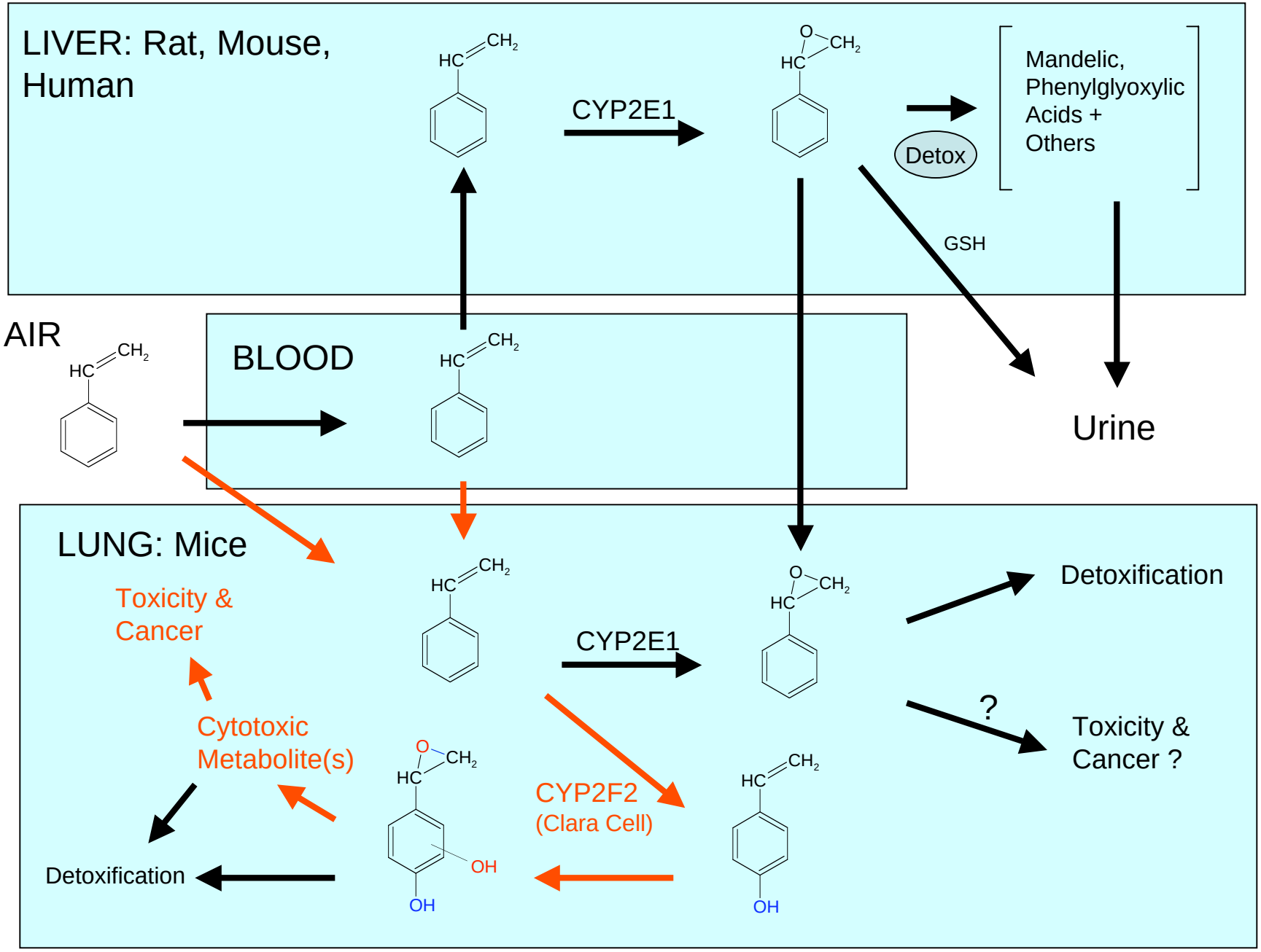
# Evidence Supporting SO MOA Hypothesis

- Styrene is metabolized to SO
- Circulating SO detected animals & humans
- *Low-level* SO-DNA adducts detected in animals and humans
- SO genotoxic in *in vitro* mutagenicity assays

# Evidence Contradicting SO Hypothesis

- Mouse lung tumors only cancer site
- Oral SO does not cause lung tumors in mice (forestomach tumors only)
- Lung tumors not related to SO in lungs
  - Inhaled carcinogenic styrene produces lung SO ~ non-carcinogenic oral SO
- SO does not explain mouse vs rat sensitivity
- SO-DNA adducts very low; not elevated in target
- Lung genotoxicity studies negative
- CYP2E1 metabolism does not impact lung toxicity

# Postulated Alternative Mode of Action of Styrene Mouse Lung Tumorigenicity



# Conclusions

- Mouse lung tumor response is not supported by the SO MOA hypothesis
- Alternative MOA hypothesis consistent with weight of evidence: *Styrene metabolism to non-genotoxic, cytotoxic ring-oxidized metabolite(s) by mouse specific CYP2F2*
- Human CYP2F metabolism unlikely